Remarks

Claims 1-16 were pending in the subject application. By this Amendment, claims 1, 4, and 14-16 have been amended, claim 6 has been cancelled, and new claims 17 and 18 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-5 and 7-18 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants and the applicants' representative wish to thank Examiner Wehbe for the courtesy of the telephonic interview conducted with the undersigned on October 19, 2004, regarding the rejection under 35 U.S.C. §112, first paragraph. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

By this Amendment, the applicants have amended claims 1, 14, and 16 to recite that the promoter sequence is a heterologous early pox promoter sequence or a non-pox virus promoter sequence. Support for these amendments can be found, for example, at page 70, lines 10-23, and page 76, lines 1-11, of the subject specification, which indicates that promoters recognized by the cellular (not poxvirus) RNA of the host cell can be used. By this Amendment, claims 4 and 15 have been amended to lend further clarity to the claimed submit matter. Support is found throughout the application. Claims 14 and 16 have been amended to recite that the cells are isolated. Support for this amendment can be found, for example, at page 12, lines 15-16 and lines 20-23, of the specification, which indicates that the vector can be introduced into cells *in vitro*. Claim 17 has also been added. Support for claim 17 can be found, for example, at page 70, lines 10-23, and page 76, lines 1-11, of the subject specification, which indicates that promoters recognized by the cellular (not poxvirus) RNA of the host cell can be used. Claim 18 has been added. New claim 18 differs from claim 1 in reciting that the vector is introduced into the cell locally, *in vivo*. Support for claim 18 can be found, for example, at page 12, lines 22-23, and in Example 11 at page 74 of the specification, which describes intramuscular injection of the entomopox virus vector.

Claims 1-6 and 8-15 have been rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 14-21 of U.S. Patent No. 6,106,825. In addition, claims 1-10 and 12-16 have also been rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 1-11 and 21 of U.S. Patent No. 6,127,172. Additionally, claims 1-10 and 12-16 have been provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 76-85, 88-89, and 101-102 of co-pending Application No. 09/662,254. The applicants respectfully assert that the claims are not obvious over the cited patents and patent application. However, in order to expedite prosecution of the subject application, the applicants have submitted Terminal Disclaimers with this Amendment, which obviate this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-16 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the subject specification fully enables the claimed invention. The applicants have addressed each of the points raised at pages 7-9 of the Office Action in turn, in the paragraphs that follow.

The applicants gratefully acknowledge the Examiner's indication that the subject application enables the *in vitro* delivery of a gene to a cell using a recombinant entomopox virus vector comprising a heterologous polynucleotide encoding the gene under transcriptional control of a promoter with early gene transcriptional activity, and an isolated cell transfected *in vitro* with the vector.

I. Promoter

At page 7 of the Office Action, it is stated that the specification does not enable the use of any and all promoter sequences, other than a promoter with early gene transcription activity. This statement appears to be predicated upon certain exerpts taken from the subject specification. Specifically, the Office Action points out that the subject specification, at pages 13-14, bridging paragraph, indicates that entomopox virus cannot productively infect mammalian cells and that gene expression is limited to early promoter activity. Further, the Office Action notes that the subject specification indicates that late poxvirus promoters, such as AmEPV spheroidin or cowpox virus ATI, are inactive in mammalian cells infected with recombinant EPV. The Office Action then

concludes that "the skilled artisan would not predict that any and all promoter sequences could express a heterologous gene of interest when encoded by a recombinant entomopox virus."

By this Amendment, the applicants have amended claims 1, 14, and 16 to recite that the promoter sequence is a heterologous early pox promoter sequence or a non-pox virus promoter sequence.

As discussed during the telephonic Examiner interview, the issue regarding enablement for the use of promoters other than those with early gene transcription activity, was also raised by the Examiner in the parent application, U.S. application serial no. 09/662,254, in which the applicants have received a Notice of Allowance. The applicants submitted an Expert Declaration under 37 CFR § 1.132 by Dr. Richard Moyer, a copy of which is submitted herewith for the Examiner's consideration. In his Expert Declaration, Dr. Moyer explains that the paragraph bridging pages 13-14 of the subject specification, which is cited in the outstanding Office Action, refers to the general observation that when using entomopox virus vectors containing entomopox promoters, genes under the control of early entomopox promoters will be expressed in a vertebrate cell, but genes under the control of late entomopox promoters will not. The applicants note that the paragraph bridging pages 13 and 14 of the subject specification cites two publications (Li *et al.* [1997] and Gauthier *et al.* [1995]), both of which describe experiments using entomopox virus vectors containing entomopox promoters. However, the distinction between "early" promoters and "late" promoters only finds context with respect to pox virus promoters (vertebrate and insect pox virus promoters). Dr. Moyer states in his Expert Declaration,

> ...when insect pox viruses infect vertebrate cells, early and only early pox virus promoters are active. This is likely because the early pox virus transcription apparatus is actually packaged within the virion particle as part of creating virions from the previous infection. In vertebrate cells, following early promoter-driven expression, the infection then crashes and eventually the input virus particles disintegrate after which the viral DNA is released into the vertebrate cell's cytoplasm; hence, the lack of late pox promoter-driven expression in vertebrate cells.

This observation is also made within the Li *et al.* publication (*Journal of Virology*, 1997, 71(12):9557-9562) at page 9557, second column, page 9560, second column, and page 9561, second

column, which is of record and was cited by the Examiner in the parent application. Furthermore, as indicated within the Li *et al.* publication at page 9561, second column, second paragraph, and at page 72, lines 25-30, of the subject specification, an exception to this phenomenon is when EPV vectors containing late pox promoters are supplied with certain factors *in trans* (*e.g.*, by co-infection with vaccinia virus), which at least partially rescue late gene expression.

Importantly, early pox virus promoters and (under certain circumstances) late pox promoters are not the only promoters that can be used in conjunction with an entomopox virus vector to achieve expression of a heterologous polynucleotide within a vertebrate cell. As disclosed at page 70, lines 10-23, and page 76, lines 1-11, of the subject specification, entomopox virus vectors containing genes under the control of non-pox virus promoters can also be utilized, as well. Non-pox promoters that are recognized by the vertebrate host cell's RNA polymerase, such as the cytomegalovirus (CMV) and herpes TK gene promoter, can be used to achieve stable transformation of the vertebrate host cell, expressing those heterologous genes that are under the control of the non-pox promoters. As disclosed at page 11, lines 28-30 and page 12, lines 1-5, of the subject specification, and as Dr. Moyer indicates in his Expert Declaration, preferred promoters are those constitutive or regulatable promoters capable of promoting sufficient levels of expression of the heterologous DNA contained in the viral vector in a vertebrate cell, such as the CMV and herpes TK gene promoters.

II. *In Vivo* Delivery

At pages 7-9 of the Office Action, it is stated that the subject specification does not provide an enabling disclosure for *in vivo* delivery of "therapeutically effective" recombinant viruses or vectors. Example 11, at page 74 of the subject specification, demonstrates the *in vivo* expression of β-galactosidase in mouse muscle using a TK-esp*lacZ* construct. The Office Action states that the working example only examines expression at day two, following injection, "and does not correlate the level or duration of gene expression with any therapeutic effect." The applicants submit that the claims of the subject application do not recite the requirement of a "therapeutic effect." Rather, the claims are directed to methods for delivering a polynucleotide encoding a protein to a vertebrate cell using the recited entomopox virus vectors and expressing the polynucleotide in the vertebrate cell, and vertebrate cells comprising such recombinant entomopox virus vectors.

Moreover, claims 1-13 are directed to the delivery of a recombinant entomopox virus vector to a cell; however, it is noted that the inventive concept pertains to the entomopox vector, useful as a tool for delivery of a gene to a cell. As such, it is noted that the specification teaches delivery of a gene to a cell using the entomopox vector of the invention in both *in vitro* and *in vivo* respects. In addition, while the present inventors were the first to demonstrate gene delivery by use of the entomopox virus vector to mammalian cells, numerous other viral vectors find readily apparent uses in the state of the art (pre- and post-filing) as a tool for both *in vitro* and *in vivo* uses. [US Patent Nos. 5,972,597; 6,312,383; 5,672,344; Kramm *et al.* (1996) *Hum. Gene Ther.* 7: 291-300; Sewell *et al.* (1997) *Arch. Otolaryngol. Head Neck Surg.* 123: 1298-1302; Cardoso *et al.* (1993) *Hum. Gene Ther.* 4: 411-418; and Podda *et al.* (1992) *PNAS* 89: 9676-9680; for example.] Furthermore, it is noted that particular effects of the transgene products in cells transduced *in vivo* are not recited in the claims.

Furthermore, Dr. Moyer indicates in his Expert Declaration that, while expression of the β-galactosidase gene was examined two days following infection with the recombinant entomopox virus vector, one of ordinary skill in the art would expect that expression of the foreign gene would be sustained beyond the two days at which the tissue was excised, particularly if other non-pox promoters recognized by the RNA polymerase of the vertebrate cells were used, such as non-pox, tissue-specific promoters. Furthermore, the experimental data set forth in Example 13, at pages 76-77 of the subject specification, which supports integration of the transgene into the cellular genome, makes longer expression more likely.

At page 8, the Office Action cites Li *et al.* (1997) for reporting the small amount of expression observed in lymphoid cells infected with recombinant entomopox virus. The Office Action states that, therefore, the skilled artisan would not predict that the entomopox viruses of the instant invention could be used to express therapeutic levels of protein in lymphoid cells, which are associated with certain disorders, such as Burkitt's lymphoma. As acknowledged at page 9 of the Office Action, the Li *et al.* publication reports experiments using beta-galactosidase enzyme under the control of pox promoters (the cowpox virus A-type inclusion (ATI) promoter and the Melolontha EPV fusolin promoter). However, as indicated by Dr. Moyer in the Declaration, the ordinarily skilled artisan would expect that entomopox virus-mediated expression of a foreign gene can be

achieved in lymphoid tissue using a non-pox promoter recognized by the RNA polymerase of the vertebrate cell, particularly if a lymphoid tissue-specific promoter is utilized. The applicants submit that choosing a tissue-specific and/or event-specific promoter or transcription element that responds to the target microenviroment and physiology for increased transgene expression at the desired site is well within the skill of those of ordinary skill in the art. Furthermore, there has been an immense amount of research activity directed at strategies for enhancing the transcriptional activity of weak tissue-specific promoters or otherwise increasing transgene expression with viral vectors. It is possible for such strategies to provide enhancement of gene expression equal to one or two orders of magnitude, for example (see Nettelbeck *et al.*, *Gene Ther.*, 1998, 5(12):1656-1664 and Qin *et al.*, *Hum. Gene Ther.*, 1997, 8(17):2019-2019, the abstracts of which are submitted herewith for the Examiner's convenience). Examples of cardiac-specific promoters are the ventricular form of MLC-2v promoter (see, Zhu *et al.*, *Mol. Cell Biol.*, 1993, 13:4432-4444, Navankasattusas *et al.*, *Mol. Cell Biol.*, 1992, 12:1469-1479, 1992) and myosin light chain-2 promoter (Franz *et al.*, *Circ. Res.*, 1993, 73:629-638). The E-cadherin promoter directs expression specific to epithelial cells (Behrens *et al.*, *PNAS*, 1991, 88:11495-11499), while the estrogen receptor (ER) 3 gene promoter directs expression specifically to the breast epithelium (Hopp *et al.*, *J. Mammary Gland Biol.* Neoplasia, 1998, 3:73-83). The human C-reactive protein (CRP) gene promoter (Ruther *et al.*, *Oncogene* 8:87-93, 1993) is a liver-specific promoter. An example of a muscle-specific gene promoter is human enolase (ENO3) (Peshavaria *et al.*, *Biochem. J.*, 1993, 292(Pt 3):701-704). A number of brain-specific promoters are available such as the thy-1 antigen and gamma-enolase promoters (Vibert *et al., Eur. J. Biochem.* 181:33-39, 1989). The prostate-specific antigen promoter provides prostate tissue specificity (Pang *et al.*, *Gene Ther.*, 1995, 6(11):1417-1426; Lee *et al.*, *Anticancer Res.*, 1996, 16(4A):1805-1811). The surfactant protein B promoter provides lung specificity (Strayer *et al.*, *Am. J. Respir. Cell Mol. Biol.*, 1998, 18(1):1-11).

At page 9, the Office Action cites the Verma *et al.* publication for the premise that sustained gene expression has been an obstacle for gene therapy. The applicants respectfully submit that the subject specification enables delivery and expression of a transgene carried by the entomopox virus vector as recited in the claims. Furthermore, although sustained or long-term expression of a therapeutic transgene is the goal of many gene therapy approaches, it should be noted that transient

expression of a transgene also has utility in biological research and in the treatment of many acute disease conditions and/or in prophylaxis. Transient gene expression may be used to promote angiogenesis during open-heart surgery, for example, by delivering a polynucleotide that, when expressed, promotes endothelial growth into parts of the heart where a normal bypass cannot be effective. In fact, under some circumstances, transient expression of a transgene encoding an angiogenic growth factor can be considered to constitute an inherent safety feature that protects the recipient from indefinite gene expression (see, for example, the abstract and paragraph bridging pages 1120 and 1121 of Baumgartner *et al.*, *Circulation*, 1998, 97:1114-1123, which is submitted herewith). In immunotherapy, it may also be desirable to provide the patient with only transient production of a transgene product, such as an immunostimulatory cytokine or immunogenic antigen. In circumstances where a viral vector is only capable of transient expression of the heterologous gene, it would be appreciated by those of ordinary skill in the art that the vector can be repeatedly administered as part of a therapeutic regimen for treatment of a chronic disease (see Manning *et al.*, *Hum. Gene Ther.*, 1998, 9(4):477-485, the abstract of which is submitted herewith for the Examiner's convenience).

At page 9, the Office Action indicates that the specification provides no guidance as to other routes or sites of injection, or dosage of virus or cells. The applicants submit that it is not necessary to specify the dosage or administration routes where such information can be obtained by one of ordinary skill in the art without undue experimentation, as is the case here. *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637, 643 (CCPA 1965). As indicated above, the claims merely recite delivery and expression of the gene. The appropriate amount of entomopox virus vector to be administered will vary with the regulatory sequences chosen, delivery route, and target tissue, and can be determined without resort to undue experimentation. Claim 18 recites that the vector is administered to the cells locally, *in vivo*.

Therefore, the applicants respectfully submit that the invention, as now claimed, is fully enabled by the subject specification. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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GPL/mv
Attachments: Amendment Transmittal Letter
Petition and Fee for Extension of Time
Three (3) Terminal Disclaimers
Copy of January 11, 2002 Declaration under 37 C.F.R. §1.132 by Dr. Richard Moyer
Nettelbeck *et al.*, *Gene Ther.*, 1998, 5(12):1656-1664, abstract
Qin *et al.*, *Hum. Gene Ther.*, 1997, 8(17):2019-2019, abstract
Manning *et al.*, *Hum. Gene Ther.*, 1998, 9(4):477-485, abstract
Baumgartner *et al.*, *Circulation*, 1998, 97:1114-1123, full text